223. A method of using the host cell of claim 221 to screen for ligand binding, comprising culturing said host cell under conditions such that a polypeptide encoded by said isolated polynucleotide is expressed, contacting said polypeptide with said ligand, and detecting binding of said ligand to said polypeptide.

224. A method of producing a polypeptide comprising culturing the host cell of claim 221 under conditions such that said polypeptide is expressed, and recovering said polypeptide.--

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 19-21 and 35-224 are pending in the application, with 19, 35, 62, 81, 96, 114, 132, 152, 169, 186 and 205 being the independent claims. Claims 19-21 and 24-28 have been withdrawn from consideration due to a restriction requirement. Claims 1-18, 20, and 22-34 are sought to be canceled without prejudice to or disclaimer of the subject matter thereof. New claims 35-224 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Support for the Amendments

The specification had been amended to correct informalities and typographical errors. The claims have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as the invention.

Support for the amendments to the specification is found throughout the specification as filed. More particularly, the specification has been amended to reposition the claim of priority benefit, to reflect the new address of the American Type Culture Collection, to comply with 37 C.F.R. § 1.821(b), and to correct typographical errors.

As requested by the Examiner, reference to sequence identifiers has been added to the brief description of Figure 4. In addition, typographical errors have been corrected. With respect to the correction on page 9, line 36, it is clear from a comparison of Figure 1 and SEQ ID NO:2 that amino acids 1 to 51 in Figure 1 correspond to amino acids -51 to -1 in SEQ ID NO:2.

With respect to the correction of the NaCl and sodium citrate concentrations on page 12, lines 24-25 of the specification, Applicants submit that 5x SSC is a well-known solution used in hybridization solutions. SSC is normally made as a 20x stock solution, and then diluted accordingly for a particular use. The 20x SSC stock solution contains 3 M NaCl and 0.3 M trisodium citrate. *See, e.g., Gibco BRL Products and Reference Guide, 2000-2001* at page 22-24 (Exhibit A). To make a 5x SSC solution, the 20x solution must be diluted by one-fourth. Therefore, a 5x SSC solution contains 750 mM NaCl (3 M ÷ 4 = 750 mM) and 75 mM trisodium citrate (0.3 M ÷ 4 = 75 mM). One skilled in the art would have immediately recognized that the amount of ingredients listed in the specification for a 5x SSC solution was incorrect. Rather than describing a 5x SSC solution, made up of 750 mM NaCl and 75 mM

trisodium citrate, the specification inaccurately listed the ingredient amounts for a 1x solution. The skilled artisan, in recognizing the typographical error, could have easily adjusted the amount of ingredients described in the specification to properly make a 5x SSC solution.

On page 12, line 26, Applicants have noted a typographical error in the amount of salmon sperm DNA. The inclusion of agents such as salmon sperm DNA as blocking agents is well known in the art. *See, e.g.,* Ausubel, *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., (1997) at page 2.10.7 (Exhibit B). One skilled in the art would know that salmon sperm DNA is present in hybridization solutions in μg/ml quantities and thus would immediately recognize the above-described typographical error in the specification. *See id.* Further, the skilled artisan, in recognizing the typographical error, could easily have adjusted the amount of ingredients described in the specification to properly included 20 μg/ml denatured, sheared salmon sperm DNA in the hybridization solution.

Therefore, because no new matter will be added to the specification if these typographical errors are corrected, Applicants respectfully request that the amendments to the specification be entered.

Support for the added claims may be found throughout the specification. Specifically, support for claims 35-46, 62-65, 81-84, 96-99, and 114-117 may be found, *e.g.*, on page 11, lines 15-24, in SEQ ID NO:1, and on page 14, line 10 through page 15, line 23. Support for added claims 47, 66, 85, 101, 119, 137, 154, 190, and 210 may be found, *e.g.*, on page 8, lines 27-29, and in Example 6, page 53, line 20 to page 54, line 15. Support for added claims 48, 67, 100, 118, 138, 155, 191, and 211 may be found, *e.g.*, on page 17, lines 7-22 and in Example 5, page 51, line 30 through page 53, line 18. Support for added claims 51, 52, 70, 71, 88, 89, 104, 105, 122, 123, 141, 142, 158, 159, 178, 179, 194, 195, 214, and 215 may be

found, *e.g.*, on page 13, lines 30-31, page 22, lines 19-33, and Example 6, page 53, line 20 to page 54, line 23. Support for added claims 60, 79, 150, 167, 203, and 223 may be found, *e.g.*, on page 33, line 3 through page 34, line 4. Support for added claims 152-153 may be found, *e.g.*, on page 11, lines 1-14, page 10, lines 1 and 2, page 12, lines 16 to 18, and page 26, lines 18 to 27. Support for added claims 169-175 may be found, *e.g.*, on page 29, line 28 through page 30, line 8, and on page 29, lines 5-8. Support for added claims 186-189 may be found, *e.g.*, on page 12, lines 19-33. Support for added claims 205-209 may be found, *e.g.*, on page 26, lines 18-27.

Accordingly, Applicants assert that the claims added herewith present no new matter.

The Restriction Requirement

The Examiner has required an election under 35 U.S.C. § 121 of one of the following groups:

I. Claims 1-18, 22, 23, and 29-34, drawn to nucleic acids, vectors, and host cells.

II. Claims 19-20, 24-25, 27 and 28, drawn to polypeptide and pharmaceutical compositions.

III. Claims 21 and 26, drawn to antibody and pharmaceutical compositions.

The Examiner contends that the subject matter of the groups set out above are distinct, each from the other.

On December 10, 1998, Applicants made a provisional election, with traverse, to prosecute the claims of Group I, claims 1-18, 22, 23, and 29-34, drawn to nucleic acids, vectors, and host cells. Applicants affirm the election of Group I. Claims 1-16 ans 20 have

been canceled, but are replaced herein by claims 35-224, which recite subject matter as defined by Group I.

With respect to the Examiner's division of the claims into three groups and the reasons stated therefor, Applicants respectfully traverse. Even assuming, *arguendo*, that Groups I-III represent distinct or independent inventions, Applicants submit that to search and examine the subject matter of all the Groups together would not be a serious burden on the Examiner. For example, publications which disclose nucleic acids normally also disclose the amino acids encoded by the nucleic acids, thereby making it a simple matter for the Examiner to search and examine polypeptides encoded by claimed nucleic acids. The M.P.E.P. § 803 (Seventh Edition, Rev. July, 1998) states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, in view of the M.P.E.P. § 803, Applicants respectfully request that all claims be searched and examined in the subject application.

Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

The Oath or Declaration

The Examiner asserts that the oath or declaration is defective, because it does not give the full name, city and state of residence, citizenship, and post office address of each inventor, as several pages appear to be missing from the Declaration filed May 11, 1998. *See* Paper No. 6 at pages 3 and 4.

Applicants submit that fully executed Declaration and Assignment documents were filed on May 8, 1998. In support of this, Applicants submit herewith copies of all documents filed on that date in response to a Notice to File Missing Parts filed on April 1, 1998 (Exhibit C), as well as a copy of the return post card stamped by the PTO acknowledging receipt of these documents (Exhibit D).

Based on the Examiner's description of the signatures on the documents, it appears that the Examiner received the first page of the Declaration and the final page of the Assignment. Based on the copies of documents returned to us by the Assignments Division, it further appears that the first page of the Assignment and the second page of the Declaration were sent to the Assignments Division. In support of this, Applicants submit herewith copies of the documents returned to Applicants with the Recordation of Assignment, dated July 14, 1998 (Exhibit E). Accordingly, Applicants respectfully suggest that the second page of the 2-page Declaration may be found in the Assignments Division.

If this document cannot be found, Applicants will submit a new Declaration in compliance with 37 C.F.R. § 1.67(a) upon allowance of claims.

Objections to the Drawings

Applicants thank the Examiner for pointing out that Figure 1 requires correction. *See* Paper No. 6, pages 4-5. Applicants will file a corrected drawing upon allowance of claims.

The Examiner has pointed out that, pursuant to 37 C.F.R. § 1.821(b), when a sequence is presented in a drawing, the sequence identifier must be used, either in the drawing or in the Brief Description of the Drawings. In response, Applicants have amended the description of Figure 4 to include reference to the sequence identifiers SEQ ID NO:6 and SEQ ID NO:7.

Rejections under 35 U.S.C. § 112, First Paragraph

(a) The Examiner has rejected claims 1, 8, 11-17, 23, and 29-33 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not provide enablement for polynucleotides encoding a DR5 extracellular domain, transmembrane domain, intracellular domain, or death domain; nucleic acids complementary to such polynucleotides; nucleic acids 95 % identical to a DR5 domain-encoding nucleic acid; or nucleic acids identical to certain nucleic acids specified in the claim, except for having at least one conservative amino acid substitution. *See* Paper No. 6, at pages 5-6.

The Examiner contends that since certain polynucleotides in the claims as filed were described by functional domain (*e.g.*, a DR5 polypeptide, or a death domain), rather than by either sequence or function, that these polynucleotides are not enabled. However, the Examiner states that "one could make and use a nucleic acid that is structurally related to a nucleic acid that has a particular sequence . . . ." *See* Paper No. 6 at page 6. While not acquiescing to the Examiner's rejection, Applicants have canceled claims 1, 8, 11-17, 23, and 29-33, and have added claims 35-46, 62-65, 81-84, 87-99, 114-117, 152-153, 169-175, 186-189, and 205-209, which describe the claimed polynucleotides by sequence.

Accordingly, this aspect of the rejection is overcome. Applicants reserve the right to prosecute the canceled claims in related applications.

(b) Furthermore, the Examiner argues that since claim 23 is drawn to a nucleic acid encoding a polypeptide having the sequence of SEQ ID NO:2, except for at least one conservative amino acid substitution, that this claim encompasses polypeptides in which no amino acids are the same as SEQ ID NO:2. *See* Paper No. 6 at page 7. While not acquiescing to the Examiner's rejection, Applicants have canceled claim 23, thereby mooting it.

Accordingly, this aspect of the rejection is overcome. Applicants reserve the right to prosecute the canceled claim in a related application.

(c) The Examiner has rejected claims 18 and 34 under 35 U.S.C.§ 112, first paragraph, because the specification allegedly does not provide enablement for a method to produce a polypeptide which is not SEQ ID NO:2 or a fragment thereof, which is not epitope-bearing. Specifically, the Examiner contends that certain claimed embodiments may not encode a polypeptide, and that others may encode a truncated or "nonsense" polypeptide. *See* Paper No. 6 at page 8. In addition, the Examiner contends that, since SEQ ID NO:2 could be encoded by a great number of nucleic acids due to the degeneracy of the genetic code, that certain claimed nucleic acids would not "resemble [a] naturally occurring encoding nucleic acid [such as] SEQ ID NO:1." *See* Paper No. 6 at page 8.

While not acquiescing to the Examiner's rejection, Applicants have canceled claims 18 and 34, and have added claims 58, 77, 93, 99, 148, 165, 201, and 221, which are drawn to host cells comprising a nucleic acid, and require that the recited nucleic acid encode a polypeptide which binds a TNF ligand. In addition, added claims 111 and 129 are drawn to host cells comprising a nucleic acid, and require that the recited nucleic acid encode a polypeptide which induces apoptosis. Finally, added claim 183 is drawn to a host cell comprising a polynucleotide which encodes and epitope. Those claims reciting (a) methods of producing a polypeptide through use of a claimed polynucleotide, and (b) methods to use a polypeptide encoded by a claimed polynucleotide, depend from the claims to host cells described above, wherein the nucleic acid contained in the host cell must encode a polypeptide with the specified DR5 activity, or encode an epitope of a DR5 polypeptide.

Accordingly, this aspect of the rejection is overcome. Applicants reserve the right to prosecute the canceled claims in related applications.

(d) The Examiner has rejected claims 1, 5-9, 14-18, and 29-34 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not provide a repeatable method for obtaining the cDNA molecule deposited as ATCC Deposit No. 97920. *See* Paper No. 6 at page 9. Specifically, the Examiner requests that an affidavit or declaration be submitted, assuring that the deposit has been made under the Budapest Treaty, and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, as required by 37 C.F.R. §1.108.

In response, Applicants submit herewith a Statement by James H. Davis, Ph.D, Esq. which provides the required assurances.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 112, first paragraph, as applied to the pending claims.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1, 8-13, 23, and dependent claims 2-7, 14-18, and 29-34 under 35 U.S.C. § 112, second paragraph, alleging that it is unclear what "DR5" means in reference to specific domains thereof. In addition, the Examiner alleges that it is unclear what the epitope-bearing portions of a DR5 polypeptide are. *See* Paper No. 6 at pages 10-11. While not acquiescing to the Examiner's rejection, Applicants have canceled claims 1-18, 23, and 29-34. Furthermore, the new claims submitted herewith recite nucleic acids, and/or fragments thereof, (a) which are related to SEQ ID NO:1, (b) which encode, or are related to nucleic acids which encode, SEQ ID NO:2, or (c) which are related to the nucleic acid of the

deposited cDNA clone contained in ATCC Deposit No. 97920. Therefore, Applicants respectfully request that the Examiner's rejection under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102

(a) The Examiner has rejected claims 8, 9, and 29-31 under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession No. Z66083. The Examiner alleges that the nucleic acid of GenBank Accession No. Z66083 would hybridize under stringent conditions to the nucleic acid encoding SEQ ID NO:2, and would reasonably be expected to encode an epitope bearing portion of the polypeptide having SEQ ID NO:2. *See* Paper No. 6, pages 11-12. According to the Examiner's alignment, sequence Z66083 aligns with SEQ ID NO:1 over a region extending from nucleotide 80 of SEQ ID NO:1 to nucleotide 275 of SEQ ID NO:1. This alignment includes a portion of the 5' noncoding region, and about 155 nucleotides of the coding region, *i.e.*, from nucleotide 130 to nucleotide 275 of SEQ ID NO:1. This region codes for amino acid residues -51 to -4 of SEQ ID NO:2, *i.e.*, the nucleic acid encoding the secretory leader sequence. *See* specification at page 8, line 30, through page 10, line 2. In order to advance prosecution, pending claims 152-153, 169-175, 186-189, and 205-209 are directed to (a) nucleic acids or fragments thereof, related to, or comprising, portions of SEQ ID NO:1 extending from nucleotide 284 to 1362, or (b) nucleic acids or fragments thereof related to, or comprising, nucleic acids encoding amino acids 1 to 360 of SEQ ID NO:2. Support for these nucleic acids and fragments thereof may be found throughout the specification, for example on page 10, lines 1 and 2, page 11, lines 15 to 27, page 12, lines 16 to 18, and page 26, lines 18 to 27.

Based on these remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b), as applied to the pending claims, be withdrawn. Applicants reserve the right to prosecute the canceled claims in related applications.

(b) The Examiner has rejected claims 8, 9, 22, and 29-33 under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AA223122. Claims 8, 9, 22, and 29-33 have been canceled. Applicants maintain that added claims 35-61, 64-65, 67-151, 155-168, 172-185, 191-204, 209, and 211-224 are novel and non-obvious over GenBank Accession Number AA223122. Applicants further assert that GenBank Accession Number AA223122 was not described in a printed publication *before* Applicants were in the possession of, in the United States, sequences relevant to the subject matter of added claims 62, 66, 152-154, 169-171, 186-190, 205-208, and 210. In support of this assertion, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Jian Ni, Reiner L. Gentz, Guo-Liang Yu, Jeffrey Y. Su, and Craig A. Rosen attesting to this fact. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a) over GenBank Accession No. AA223122.

Based on these remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(a), as applied to the pending claims, be withdrawn. Applicants reserve the right to prosecute the canceled claims in related applications.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 8, 9, 22, and 29-34 under 35 U.S.C. § 103(a) as being unpatentable over GenBank Accession No. AA223122 and Chinnaiyan, *et al.*, *Science 274*:990-992 (1996), in view of WO 94/01548. The Examiner asserts that since Chinnaiyan *et al.* teaches expression of a DR3-encoding polynucleotide, and WO 94/01548 teaches the

desirability of expressing ESTs, that these references, in combination with the EST disclosed as GenBank Accession No. AA223122, renders the above-mentioned claims obvious.

Applicants have asserted, *supra*, that added claims 35-61, 64-65, 67-151, 155-168, 172-185, 191-204, 209, and 211-224 are novel and non-obvious over GenBank Accession Number AA223122, and that GenBank Accession Number AA223122 was not described in a printed publication before Applicants were in the possession of, in the United States, sequences relevant to the subject matter of added claims 62, 66, 152-154, 169-171, 186-190, 205-208, and 210. The remaining references cited by the Examiner do not establish a *prima facie* case of obviousness, because there is no teaching of a polynucleotide comprising a nucleic acid, or a fragment thereof, which encodes a DR5 polypeptide. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the three references cited by the Examiner, be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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